REMARKS

The official action of 13 July 2010 has been carefully considered and reconsideration of the application as amended is respectfully requested.

The courtesy of Examiner James Anderson in conducting a telephone interview with C.G. Wang, Tom Vullo and Applicants' undersigned representative on 20 October 2010 is noted with appreciation. The Interview Summary mailed 25 October 2010 accurately reflects what transpired in the interview. In particular, the Examiner suggested that, to overcome the rejection of record, Applicants should show that one of skill in the art would not have been motivated to combine the cited prior art references to arrive at the claimed invention. Applicants discuss the absence of motivation below.

The claims have been amended to remove the bases for the rejections under 35 USC 112, second paragraph. In particular, claim 115 has been amended to make clear that the recited dose refers to the dose of emission of Auger electrons (see specification at, e.g., the first sentence of paragraph [0011]). Claim 115 has also been amended more clearly to distinguish over the prior art with the recitation that the emission of the Auger electrons results in release of hydrolytic enzymes in the lysosomes (see specification at paragraph [0063] and discussion below).

The claims stand rejected under 35 USC 103(a) as allegedly being unpatentable over Dees et al and Cash et al in view of Laster et al. Applicants respectfully traverse this rejection.

The claimed invention is based at least in part upon Applicants' discovery that an *in situ* dose of Auger electrons that are effective at very, very short distances only can be used to cause the death of tumor cells by a **chemotherapeutic** method. Specifically, Applicants have discovered that the desired effect of killing tumor cells can be accomplished by disruption of lysosomes within the cells to cause release of the lysosome

contents with a change of cytoplasmic pH within the cells whereby to cause cell death in a chemotherapeutic manner.

Lysosomes are very small entities of a single cell; they are totally different from an organ. The claimed invention calls for resonant scattering for inner shell ionization, an Auger cascade, and *in situ* Auger electrons to generate the Mega-Gray to cell organelles that take up Rose Bengal. Lysosomes appear in all mammalian cells except for red blood cells and they are membrane-delimited organelles containing a high proton concentration ($pH \leq 5$) and having more than 40 hydrolases with a pH optimized much below 6. They engage in the degradation of macromolecules taken up in extra-cellular space (endocytosis) such as the uptake of Rose Bengal molecules. Leaky tumor cells with a less defined plasma membrane morphology appear to incur more endocytotic uptake of molecules like Rose Bengal. The disruption of lysosomes with release with their contents initiates localized chemotherapy for a cellular pH change with resultant cell death.

In line with the above, the principle of operation for the use of Auger electrons, as in the claimed method, is fundamentally different than the principle of operation for the use of X-ray intensifiers or photosensitizers as in the primary reference cited by the Examiner (Dees). The claimed invention relies on resonant scattering for inner shell ionization and the production of an Auger cascade that leads to *in situ* emission of Auger electrons. Auger electrons, with only 12-18eV of energy, would deposit **all** their ionizing energies within a few atomic distances, or very large Linear-Energy Transfer ("LET") under a few nanometers. It would deliver 10^6 Gray to its neighboring medium because Gray is calculated only in the cm^3-scale. But, the Auger electrons would deliver absolutely no harm beyond the immediate neighbor. In other words, if measured in conventional radiological terms as the dose for a tissue instead of for the organelles of a cell of the tissue, it has no effect; or nearly zero Gray with no LET beyond the distance of a few atomic diameters and no tissue damage according to the conventional dose scale.

In contrast to resonant scattering as in the claimed invention, the principle of operation of the primary reference, Dees, is the use of an intensifier/photosensitizer for

enhanced photon scattering cross section. There is a fundamental difference between an intensifier for enhanced photon scattering and resonant scattering. The enhanced ionization in conventional radiology, measured in 10-20 Gray, is fundamentally different from the resonant scattering for inner shell ionization leading to *in situ* Auger electrons that are measured in $10e^6$ (1 million) Gray in a very small dimension that does no damage anywhere in the cell except to the DNA and lysosomes. 10 Gray over the size of a few cells or $10e^6$ Gray over the thickness of the fraction of a lysosome membrane are two entirely different modes of action and one of skill in the art would not treat them in the same manner.

For conventional radiation therapy, as in Dees, the ionization range is selected **to reach** the diseased tissue that is being treated. In the absence of a recognition that cell lysosomes can be used as a chemotherapeutic agent, there would have been no motivation or reason **to limit** the sphere of damage of Dees' radiation to a very small ionization area through the use of an Auger effect. Accordingly, there would have been no motivation or reason to modify Dees in the manner proposed by the Examiner as this would impermissibly change the principle of operation of the reference. See MPEP 2143.01(VI) ("If the proposed modification or combination of the prior art would change the principle of operation of the prior art invention being modified, then the teachings of the references are not sufficient to render the claims prima facie obvious.").

For the above reasons, Applicants respectfully submit that the references cited by the Examiner cannot be properly combined and thus cannot set forth even a *prima facie* case of obviousness for the invention as defined in any of the claims as amended. Moreover, Applicants respectfully submit that, even assuming for the sake of argument that the references were properly combinable, the results that can be obtained with the claimed method (disruption of lysosomes with release of their contents and cell death as a result of this release) could not have been predicted from the cited art in the absence of any recognition of this principle of operation. Accordingly, the results that can be achieved with the claimed method must be considered to be unexpected and sufficient to rebut any alleged *prima facie* case of obviousness set forth by the cited art.

With specific respect to claims 125, 126, 139, 140, 146 and 147, Applicants respectfully submit that these claims are additionally patentable over the cited art. In this respect, Cash teaches that the contrast agents described therein will only be present for a relatively brief period such that the therapy described therein should be performed within a half-hour after injection of the iodine (Cash at column 7, lines 47-52). Dees suggests that, with the method described therein, wait times of hours or days for clearance of a radiosensitizing agent can be avoided (Dees at column 2, lines 52-55). In other words, the cited art teaches away from the timing of irradiation recited in these claims.

In view of the above, Applicants respectfully submit that all rejections and objections of record have been overcome and that the application is now in allowable form. An early notice of allowance is earnestly solicited and is believed to be fully warranted.

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Respectfully submitted,

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